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Amaurotic Family Idiocy

(Tay-Sachs Disease)

Inaugural-Dissertation

zur

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Historical Introduction

In 1881 the English Eye specialist, Warren Tay, reported the finding of a cherry red spot in the fundus of a Jewish infant 12 months of age. (13) Six years later, Bernard Sachs, a New York physician, reported a case under the heading «Arrested Cerebral Development», and gave a classic clinical and pathological description of what he called infantile amaurotic family idiocy. (2)

Sachs was the first to recognize the significance of the cherry red spot, although at the time of his first report he considered the disease in his case to be an isolated instance of idiocy associated with amaurosis. (11) Four years later there was another instance of the disease in the same family in which identical changes in the brain were observed at autopsy. By 1896 Sachs had seen eight patients with the disease, and recognizing the familial factor, he applied the name amaurotic family idiocy to the condition which he also termed agenesis corticalis. Since then the syndrome has been called amaurotic family idiocy or Tay-Sachs disease.

As the name indicates, it is familial, and as rule occurs among Jews, very often when the parents are cousins. Jewish families migrating from the Polish provinces and formerly belonging to the Russian Empire are those most often affected (4). In exceptional cases non Jews are affected however. Carter was the first to observe that in most cases the disease had occured in Jews (5). The literature has an instance of a Chinese child afflicted with the disease (9).

Pathogenesis

Amaurotic family idiocy is a heredo-degenerative disease and belongs to the lipoidosis. It is particularly related to Niemann-Pick's disease, a constitutional anomaly of lipoid metabolism. (1) When the localisation of the anomaly is restricted to the brain, we have the pure type of amaurotic family idiocy, characterized by enormous accumulations of phospholipids in the glia and in the nerve cells with its subsequent degeneration. The subsequent demyelinization which occurs is mostly confined to the cortex and the sub cortical U fibers. However when this metabolic anomaly is restricted to the liver and spleen we have the purest form of Niemann-Pick's disease (hepatospleno-megaly) characterized by the accumulation of phospholipids in the reticulo-endothel cells of these organs.

There are however clear transitional cases showing the localization in both systems, and finally the lipoid accumulation may occur almost everywhere.

Amaurotic family idiocy must therefore be regarded as a special phase within a generalized disturbance of lipid metabolism, the Niemann-Pick's

disease. It is a question of how widespread the localization of the metabolic disorder is.

Many theories have been offered but the most tenable is that furthered by Thannhauser and Magendantz. (10) According to these authors the mechanism causing the so called lipoidosis is an intracellular disturbance of the lipid metabolism. In support of their thesis, they point out that the hypercholesteremia is found in only one type of xanthomatosis and normal plasma values for cerebrosides are found in Gauchers disease and normal values for sphingomyelin in Niemann-Pick's. The lipid substances which accumulate in the body cells in these conditions are not supplied from the abnormal quantities in the blood, but originate from the cell and are obtained abnormally by it.

Neutral fats, lecithin, and cephalin are absorbed from the intestines and are mainly supplied to the blood stream by way of the thoracic duct. The levels of these lipids in the blood stream are influenced therefore by the various factors which influence fat absorption and metabolism. Sphingomyelin, cholesterol and cholesterol esters on the other hand do not depend on intestinal absorption and are supplied to the blood stream chiefly through cellular metabolism of organs and are present in the serum in neglible amounts, since they tend to remain in the cells in which they are formed.

Histo-Pathology

Macroscopically: The brain may show no gross changes or malformations (7). It usually seems hard to the touch and of leathery consistence. The cerebellum is often very small and firm. The brain in weight is usually reduced.

Microscopically: There are universal changes in the ganglion cells throughout the entire central nervous system, hemisphere, brain stem, pons, medulla, cerebellum and spinal cord as well as the retina. The cells are swollen and assume varied globular shapes; they may be bottle shaped, pyriform or round. The dendrites are swollen and enlarged and ballon like in appearance. The cell nuclei are well preserved and are displaced to the periphery, although at certain stages they disintegrate. The Nissl bodies may be normal but are found only in the area surrounding the nucleus. The neurofibrils are intact but are diplaced to the periphery. Associated with widespread changes in the ganglion cells are the destruction of the cortical myelinated fibers and the proliferation of the glia cells which make the cortex very cellular. There are no changes in the blood vessels and no evidence of an inflammatory process.

In the retina the process is identical with that of the brain. The ganglion cells which are numerous in the area of the macula become swollen and finally necrotic, which causes the retina to appear dirty white or grayish white. The fovea contains no cells and therefore remains transparent, so that the choroidal blood vessels remain visible. As a result there is a small red spot, the fovea surrounded by an edematous and necrotic zone, grayish white in color, which is called the cherry red spot. The optic nerve shows secondary degeneration.

Biochemistry of the phospholipids and their distribution in the central nervous system

The phospholipids have been separated into three distinct substances: lecithin, cephalin and sphingomyelin (6). All three contain the elements nitrogen and phosphorous beside carbon, hydrogen and oxygen. In lecithin and cephalin the N/P ratio is 1 :1 and in sphingomyelin it is 2 : 1. Sphingomyelin yields on hydrolysis fatty acid, phosphoric acid, choline and another nitrogenous base, sphingosine. No glycerol is found in sphingomyelin.

The chief constituent of the myelin sheath is actually a mixture of substances. The principale lipid constituents are free cholesterol, cerebroside and sphyingomyelin, rather than cephalin and lecithin as was thought at one time. The distribution of lipids in the peripheral nerves resembles that of lipids in the white matter of the brain, rather than that of the gray matter. Both brain white matter and peripheral nerves contain more cerebroside, free cholesterine and sphingomyelin than brain gray matter.

Clinical features and course:

The onset is usually at four to six months of age. The first symptom noted as a rule is listlessness in a previously healthy and otherwise normal infant. Progressive muscular weakness develops, with a loss of muscular power. As time goes on the infant can no longer change its position and is unable to hold its head up or sit up even when placed in a sitting position. Finally he becomes helpless, lying apathetically in his crib. Vision is impaired and then blindness occurs. (2)

With progression of the disease the hearing becomes unusually acute (hyperacusis) and at the slightest noise the infant may be startled even though it was apathetic and drowsy a moment before. Bouts of explosive laughter and frequently in the terminal stages other symptoms may appear which overshadow the picture. These are muscular twitches as well as clonic muscular contractions of the eyelids or of the extremities or as convulsions of a few seconds duration in response to external stimuli (auditory or tactile).

The most striking feature is the visual disturbance which is due to changes in the retina or optic nerve. All patients become blind. Cherry red spot and in addition optic atrophy is frequently encountered. Although the cherry red spot is not always encountered other changes have been reported.

Later in the course of the disease the child may become marantic, it refuses food, is unable to nurse and has difficulty in swallowing, which necessitates its being fed by gavage. Emaciation develops rapidly in the later stages (8). Death usually occurs from marasmus or from an intercurrent infection such as broncho-pneumonia or sudden cardiac failure. The age at which death occurs is on the average 18 months or by the time the child is two years of age.

Other forms of amaurotic family idiocy

There are three forms of amaurotic family idiocy; the early juvenile, the juvenile and the adult form.

1) The early juvenile form:

Bielschowsky described this form of cerebromacular degeneration (3). The onset is at three or four years of age. The red spot in the macula is usually absent but the optic nerve is pale and atrophic and the region of the macula is degenerated.

2) The juvenile form:

The clinical features of the juvenile form exhibit progressive loss of the intellectual faculties, loss of vision and loss of motor power (3). This condition differs from Tay Sachs in that the cases do not occur predominately in the Jewish race, that blindness is not associated with the same typical picture of the fundus, and that the first clinical manifestations appeared at a later age and the progress was slower.

3) The adult form:

In the adult form the clinical picture is not so sharply defined (12). There are mental symptoms, convulsions, cerebellar manifestations and atrophic muscle changes. Disturbances of vision and the cherry red spot in the macula are foreign to the picture of the adult form. The histopathology is distinctive and diagnostic. It consists of the characteristic lipoid filled ganglion cells (Schaffer cell disease) in small groups or singly throughout the nervous system, especially in the cerebellum.

Therapy

Although all attempts of treating amaurotic family idiocy have proved futile there have been instances of using drugs in the most recent investigations in an attempt at a cure if not a prolongation of the life of the child. ACTH has been one such drug.

Theoretically the basic derangement of Tay Sachs disease is a defective cell which is incapable of assimilating lipoid material (7). Connand Adelsberg using this fact as a premise, and knowing that there is a close relati onship between the adrenal cortex and lipoid metabolism, took this foregoing consideration and carried out the following work.

ACTH was administered for a period of 20 days with the dosage ranging from 25—50 mg. The patient was a Hebrew infant with quite typical findings of the disease.

Results: The changes in the urinary excretions of hormones, blood glucose, number of circulating eosinophiles were indicative of a normal reactive adrenal cortex. Therefore a disturbance of the adrenal cortex may be excluded as an etiological factor.

The initially elevated lipoid phosphorous was reduced approximately 60 %. Serum cholesterol was also reduced under therapy. Clinically no significant changes were observed.

Physical Examination

It disclosed a one year old child corresponding in length to its age, fairly heavy and who was in constant movement. He couldn't sit by himself nor could he stand. The skin was clear. The lymph nodes were small, movable and indolent. The thyroid was normal and without nodes. The head was somewhat enlarged with a moderate caput quadratum and distinct round cranium. The fontanella was not as yet closed, it was however quite firm to the touch. Tension was not increased. The vertebral column was straight. Extremities normal. The lungs were normal to auscultation and percussion. The abdomen was not remarkable. The genitals were male and infantile. There was a distinct hypoplastic phimosis of moderate degree with a micropenis. Cryptorchidism was present without palpable testis. The scrotum was very small and empty. The motility and sensibility were normal. The reflexes were difficult to elicit, but bilaterally the abdominal reflexes were absent. Babinski was negative and clonus was not elicited. The plantar right reflex was distinct. The eyes occasionally displayed a distinct convergent strabismus. The pupils were round, isocoric and they reacted distinctly to light and convergence. Sclerae were white.

History:

It was disclosed that the pregnancy had run a normal course. The mother was not sick during this time. She was delivered at term. In 1950 without instrumentation she was aborted in the first few months of pregnancy. Three months after the birth of the first child (1949) the mother had a peritonitis, and for that reason she was hospitalized. Twice after that she had peritonitis and for that reason was eventually operated upon. The childs's father was in good health.

At the age of 10 months the child had pneumonia and at 4 months he had a questionable asthma attack. According to the mother the child was always retarded compared to other children his age. He never made normal progress and the mother doubted if the child could see well, but in any case it didn't see everything.

Upon admission it couldn't as yet sit and couldn't stand alone without a moderate amount of support. It couldn't as yet walk.

Laboratory:

Blood: Hb 90 %, RBC 5 000 000, WBC 9 000. Segmented 24, Juveniles 1, Eos. 4, Lymphs. 67,5 %, Monos 3,5.

Lumbar puncture: The pressure was somewhat raised. The chemistry and the cells were not done since the fluid was grossly bloody from the tap.

Skull X-ray: Normal, and the Sella was within normal limits.

Lumbar puncture: Pressure normal, color clear and the Pandy was negative. Haine 69 mg%, Cells 5/3. Wassermann negative and Goldsol negative.

Blood serum determinations: Ca. 11,2 mg%, Phosphorus 5,9 mg%, Phosphate 4,8 Units, Wasserman negative. 17 Ketosteriods in urine 570 mg%. In 297 ccm of urine a total of 1,7 mg%. This figure was essentially too high for a child of one year. Vertebral column marrow puncture: Scarcely any elements outside of normal megakaryocytes were found.

The intelligence test revealed an I.Q. of. 59, 7.1 test age.

Therapy and course:

The child was given as a sedative daily, magnesium sulfate, calcium bromate and phenobarbital solution. Further he received one ampulle of Benadon as well as three times a day one tablet of glutamic acid. For treatment of the genital defect one ampulle of Pregnyl three times a week was given. Furthermore as stimulant therapy intramuscular injections of milk were tried, until the total amount per dose was 4 ccm. The fever thusly produced reached exactly 40° C. As a consequence of the combined therapy the child was essentially quieter, the hypermotility, especially in the area of the extremities, dissappeared almost entirely, and in the region of the head was essentially more discrete. The child became much more responsive and was much oftener found laughing and in good humor. As a result of the Pregnyl medication there was prompt descensus of the testis bilaterally. The administration of Di De was given, upon which three teeth broke through. Since the child had immeasurably improved he was released with instructions to the mother to bring him back for periodic checkups.

A few months later he was brought to the Jenner Spital for readmission and was found to be restless, much more so than upon his admission in Nov. 1953. The hands carried out continous seeking movements and the head shook back and forth. The examination of the central nervous system was essentially the same as before. This time an examination of the eye grounds was carried out. It showed the bulbus to be of normal size and to be parallel in rest as well as movement. The pupils were round and reacted to light and convergence. The child couldn't fix as yet and from time to time a horizontal pendulous nystagmus was noticed. The visus was almost zero. The papillae of both eyes were atrophic and white with no pigment in the periphery. The macula was not remarkable and the vessels were of normal caliber. Also on the occasion of the second admission blood serum determinations were carried out. The A/G was normal. Ca and P were also normal. Total Cholesterol was 224 mg%. Cholesterol ester 194 mg%. Total Lipoid 994 mg%. All other examinations yielded the same results as at the time of the first admission.

At this time the diagnosis of amaurotic family idiocy was seriously considered, since the amaurosis and the idiocy were the outstanding features of the disease picture. It was thought that it could possibly be an early stage without the cherry red spot or a case entirely without macula changes. These considerations led to a sternal puncture in the hope that lipoid storage cells could be demonstrated, since the cholesterine and lipoid of the serum were raised. None were found. The child was released shortly thereafter.

In May the child was again admitted with a fever of 41°C. With the increase in fever the patient became extremely stiff and cramped to the point of clonic tonic contractures. The blood serum determinations were once again carried out with the results similar to the tests two months previous. A sternal puncture was again performed but yielded no new evidence. The diagnosis was still maintained as lipoidosis in the sense of a Tay Sachs amaurotic family idiocy.

Summary

A male child of one year was admitted to the Jenner Spital in Bern due to his mother's complaint that he was retarded as compared to other children his age, and she believed that he was unable to see well. Physical examination revealed a child who was in constant movement, whose reflexes were difficult to elicit, but equal, optic nerve atrophy and bilateral cryptorchism. Laboratory examination showed an increased total lipoid content of 994 mg%. The intelligence test revealed an I. Q. of 59. The child was treated symptomatically with improvement, and then released. He was readmitted a few months later with an exacerbation of symptoms. At this time lipoid storage cells in the bone marrow was sought for but without success. The child showed no improvement with all the therapy employed. The optic nerve atrophy, the idiocy and the raised blood serum lipoid pointed to a diagnosis of a lipoid storage disease in the sense of a Tay-Sach's amaurotic idiocy.

The familial character of Tay-Sach's disease in this case cannot be ascertained. The mother has but one other child and he is in good health. On the basis of two children the demonstration of a familial tendency is not justified.

The absence of macula changes does not speak against the presence of amaurotic family idiocy. The literature cites such instances.

Summary

At the end of the last century Tay and Sachs concurrently described a disease associated with blindness and idiocy. They both observed that it was predominately familial, hereditary and occurred in the Jewish race. Amaurotic family idiocy belongs to the lipoidosis with the localization in the brain cortical cells and the ganglion cells of the retina. There is a complete degeneration of the affected cells with a subsequent glial proliferation.

The child is usually affected at about the sixth month of life, progressive motor weakness being the predominating symptom. Other central nervous system symptoms intervene such as hyperacusis, clonic contractures and then finally total blindness. Death generally occurs at the age of two years from marasmus or some intercurrent infection.

Treatment has been futile, with the latest drugs proving to be of no avail.

The purpose of this paper has been to review the literature and present the pathology, history and clinical features of this disease. One case has been presented.

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